

# STUDY ON CRYSTALLINITY AND COMPACTIBILITY OF BINARY MIXTURE OF ANALGESIC SUBSTANCES WITH MICROCRYSTALLINE CELLULOSE

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## STUDY ON CRYSTALLINITY AND COMPACTIBILITY OF BINARY MIXTURE OF ANALGESIC SUBSTANCES WITH MICROCRYSTALLINE CELLULOSE

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## ABSTRACT

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**Objectives:** The aim of this study was to investigate crystallinity and compatibility transformation of two binary mixtures of analgesic substance with excipient due to mixing and compression.

**Methods:** Analgesic substances used in this study were 10-mefenamic acid (MA) and acetaminophen (AC). Each substance was mixed with microcrystalline cellulose 9 excipient with drug-excipient ratio of 70:30, 80:20 and 90:10 %w/w then compressed with pressure of 29.4 kN. Characterization was done by Powder X-Ray Diffraction (PXRD), thermal analysis (DTA), FTIR spectrometer and a Scanning Electron Microscope (SEM). Mechanical properties was also evaluated by calculating its tensile strength

**Results:** Evaluation of crystallites size of MA and MA-MCC mixture showed that the value of MA crystallite size is relatively fixed in all the peaks observed.

Crystallite size of the AC and AC-MCC mixture also showed similar results with MA. From the elastic modulus curve, it was recognized that the tensile strength of MA is greater than AC, it indicates that the MA is more plastic than AC.

**Conclusion:** X-ray powder diffraction of binary mixture indicated that intensity of both MA and AC decreased with increasing amount of MCC. The average crystallite size were 15-19 Å (MA) and 21-30 Å (AC). It was known that MA has compactibility better than AC.

**Keywords:** Mefenamic Acid, Acetaminophen, Microcrystalline Cellulose, Crystallinity, Compactibility.

## INTRODUCTION

Tablets are the most widely used solid preparation with several advantages in term of administration, formulation and manufacturing [1]. Tablet preparations involve mixing and compression of active substance and excipients [2]. During compression the individual crystallite of each component could undergo rearrangement then having deformation or fracture. This deformation influenced by the arrangement of molecules within the crystal lattice, intermolecular interactions which provides rigidity in the crystal lattice, and the crystal defects or damage and the crystal orientation due to compression forces [3]. Compression process often lead to change the properties of drug substance and excipients such as particle size, specific surface area, crystallinity, polymorph, crystal habit [1].

Analgesic and antipyretic drugs are extensively produced in tablet dosage form. Mefenamic acid (MA) is non-steroidal anti-inflammatory drug (NSAID) derivatives of amino antranilate. MA has a melting point of 230°C followed by decomposition [4,5,6]. During manufacture, MA tablets often cause capping or sticking. Acetaminophen (AC) generally has brittle fracture property. Its brittle fracture character is associated with inappropriate movement of the crystal lattice. The difference of crystal orientation also affects the mechanical properties and morphology of the crystals therefore it can be used to predict the mechanical properties of crystal structure of tablet [3]. Microcrystalline cellulose (MCC) is commonly used as binder or filler in tablet and capsule dosage forms prepared by wet granulation or direct compression. MCC can also serve as a lubricant and disintegrant in tablet dosage form [7]. MCC can be consolidated into more compact mass compared to other materials when compressed with same compression force.

Mechanical strength of tablet was affected by interaction of the materials properties, reduction of materials volume, materials properties, main bonding mechanism and surface area where the bonding occurs. During compression, microcrystalline particles exhibit both elastic and plastic deformation. Hydrogen bonding and mechanical bonding are dominant mechanism in tablet manufacture, while the solid bridges are assumed not commonly occurs [8,9].

This study was performed to determine the transformation of crystallinity and compatibility of binary mixture of MA/AC and MCC that is subjected to compression.

## MATERIALS AND METHODS

## Materials

MA and AC was procured from PT.Kimia Farma, Jakarta, Indonesia, microcrystalline cellulose (MCC) was obtained from Asahi Chem. Co, Kansei, Japan.

## Methods

Physical mixture MA - MCC and AC - MCC with a ratio of 90:10, 80:20 and 70:30 (% w/w) was compressed using hydraulic press with diameter of 13 mm flat punches and compression force of 29.4 kN, equivalent to 3,000 kgf (Braseby - Specac, Germany). Characterizations were done by powder X-ray diffraction (PXRD), differential thermal analyzer (DTA), infra-red spectrometry and scanning electron microscope (SEM).

## Powder X-ray Diffraction Studies

Powder X-ray diffraction patterns were obtained using a X-ray diffractometer (Philips X'Pert, Netherland) with CuK $\alpha$  radiation (1.54 Å), at 40 kV, 30 mA, passing through a nickel filter with a divergence 2 $\theta$  (0.5°), antiscattering slit (0.5°), and receiving slit (0.15 mm), scanned at a rate of 2.4°/min, over the 2 $\theta$  range of 5-40°. Obtained diffractograms were analyzed with Winplotr diffraction software. Crystallite size was calculated using the Scherrer's equation:

$$D = k \lambda / \beta \cos \theta \quad \text{Eq.1}$$

Where, k varies from 0.89 to 1.39, with assumption: k = 1, wavelength of X-rays  $\lambda$  = 0.1541 nm and  $\beta$  is integral breadth [9].

## Mechanical Properties

30 mg of pure substances and binary mixture were compressed using hydraulic press at different kgf/cm<sup>2</sup> for 1 min. Tablets were stored in desiccators for overnight to allow elastic recovery. Thickness and diameter were measured for each tablet. Hardness of

tablets were measured using Erweka hardness tester. Tensile strength ( $\sigma$ ) ( $\text{kgf/cm}^2$ ) was calculated using following equation [10].

$$\sigma = 2F/\pi Dt \quad \text{Eq.2}$$

where, F= hardness (kgf), D = tablet diameter (cm) and t = thickness (mm).

#### Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra were measured using Spectrum One, Perkin Elmer, USA. Sample were dispersed in KBr powder and compressed 29.4 kN. FTIR were recorded from 4000 – 400  $\text{cm}^{-1}$ .

#### Differential Thermal Analysis Studies

Differential thermal analysis was performed on a differential thermal analyzer (Mettler Toledo FP 85, Switzerland) which calibrated with indium. 5-10 mg of pure substances and mixture of

MA: MCC and AC: MCC with ratio of 70:30 (% w/w) were heated in hermetically sealed aluminum pans with a heating rate of 10°C/min at temperature of 50 - 300°C.

#### Scanning Electron Micrograph

The tablet surface and fracture of pure substances and mixture of MA : 11 and AC : MCC with ratio of 70:30 (% w/w) were observed with scanning electron microscope (SEM) JEOL, JSM-840A, Japan Electron Optics Limited, Japan with magnification of 500 times.

#### RESULTS AND DISCUSSION

The results of X-ray diffraction MA, AC and combination with the MCC were shown in Figures 1 and 2. X-ray diffraction peaks MA at  $2\theta = 6.2^\circ, 26.2^\circ, 27.7^\circ$  and X-ray diffraction peaks AC at  $2\theta = 12.1^\circ, 26.5^\circ$  and  $32.6^\circ$  used further for calculation of the intensity and crystallite size.

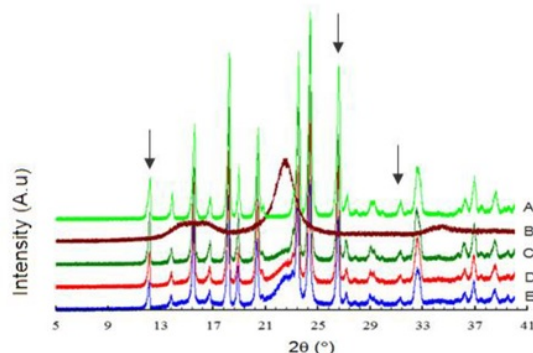


Fig. 1: X-ray diffractograms of A. MA, B. MCC, C. MA-MCC (90:10), D. MA-MCC (80:20) and E. MA-MCC (70:30) %w/w.

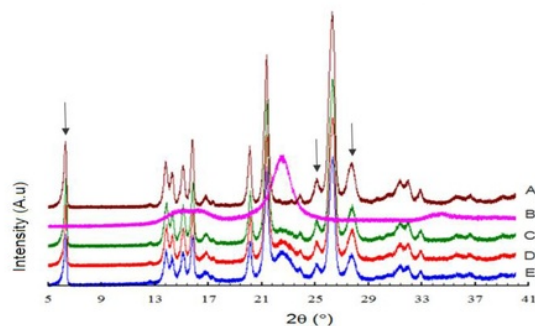


Fig. 2: X-ray diffractograms of A. AC, B. MCC, C. AC-MCC (90:10), D. AC-MCC (80:20) and E. AC-MCC (70:30) %w/w.

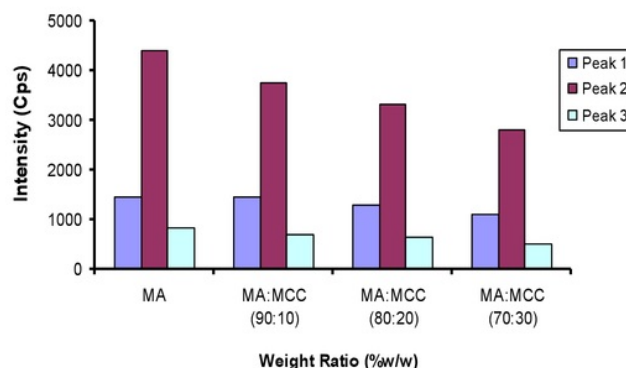


Fig. 3: Intensities from three peaks with different MA-MCC weight ratio.

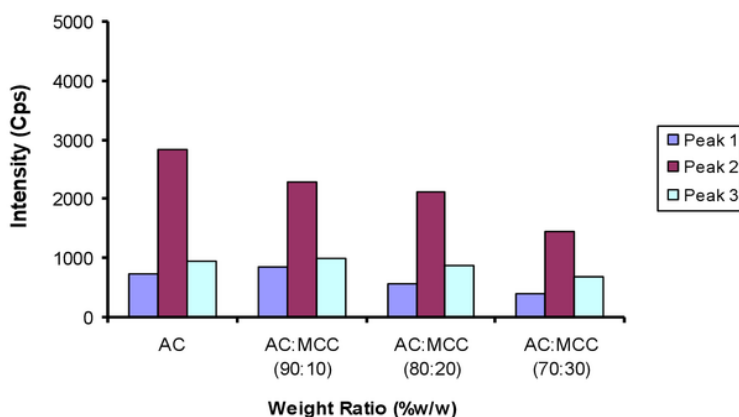


Fig. 4: Intensities from three peaks with different AC-MCC weight ratio.

Fig. 3 and Fig. 4 showed that MA and AC intensity values decrease in all observed diffraction peaks correspond to MCC amount added in the mix. It indicates that increasing amount of MCC led to intensify MA crystal disorder. MCC is capable to blockade the formation of the crystalline regularity of MA and AC, so potential energy of molecular bond becomes smaller. MA has high hydrophobicity properties therefore; it tends to stick on the surfaces, which cause problems

during granulation and compression [11]. In case of AC, this substance has two polymorphic forms. Polymorph form I (monoclinic) is thermodynamically stable but tends to form unstable and capping mass due to the rigid construction of the molecules in crystal. Form II (orthorhombic) exhibit better compression properties but it could be transformed into form I during manufacture process [2].

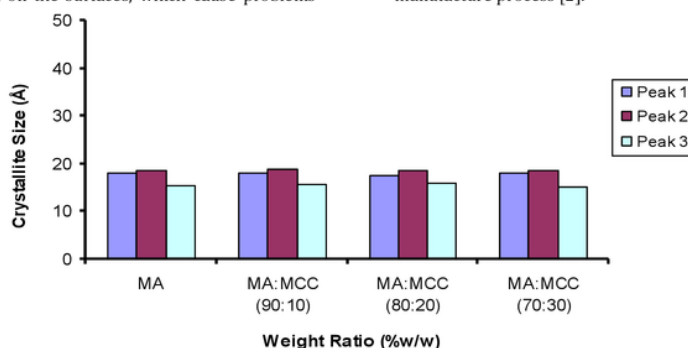


Fig. 5: Crystallite size from three peaks with different MA-MCC weight ratio.

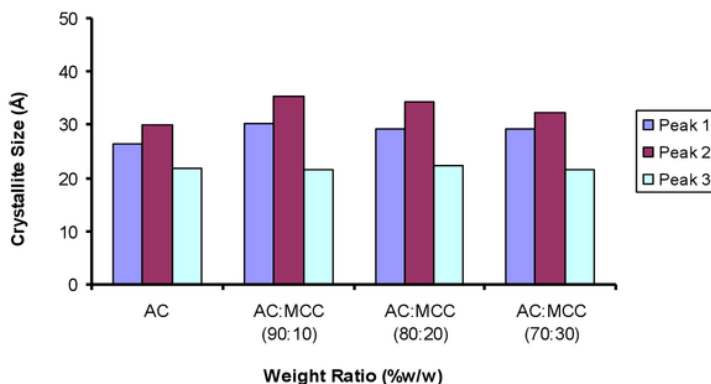


Fig. 6: Crystallite size from three peaks with different AC-MCC weight ratio.

Evaluation of crystallites size of MA and MA-MCC mixture showed that the value of MA crystallite size is relatively fixed in all the peaks observed. Peak 1 ( $2\theta = 6.2^\circ$ ) on field 1 0 0 gives crystallite size from 17.5 to 18.2 Å. Peak 2 ( $2\theta = 26.2^\circ$ ) on the field 0 2 1 has a crystallite

size from 18.8 to 18.8 Å and peak 3 ( $2\theta = 27.7^\circ$ ) on field 4 1 0 has a crystallite size 15.2 - 15.9 Å. Ratio difference of the mixture has no effect on the size of crystallites MA with the compression of 29.4 kN (Fig. 5).

The evaluation of crystallite size of the AC and AC-MCC mixture also showed similar results with MA. Peak 1 ( $2\theta = 12.1^\circ$ ) on field 1 2 0 gives crystallite size from 26.5 to 30.2 Å. Peak 2 ( $2\theta =$

$26.5^\circ$ ) on the field 0 2 2 has a crystallite size from 30.1 to 35.5 Å and peak 3 ( $2\theta = 32.6^\circ$ ) on the field 0 6 0 has a crystallite size 21.7 - 22.5 Å (Fig. 6).

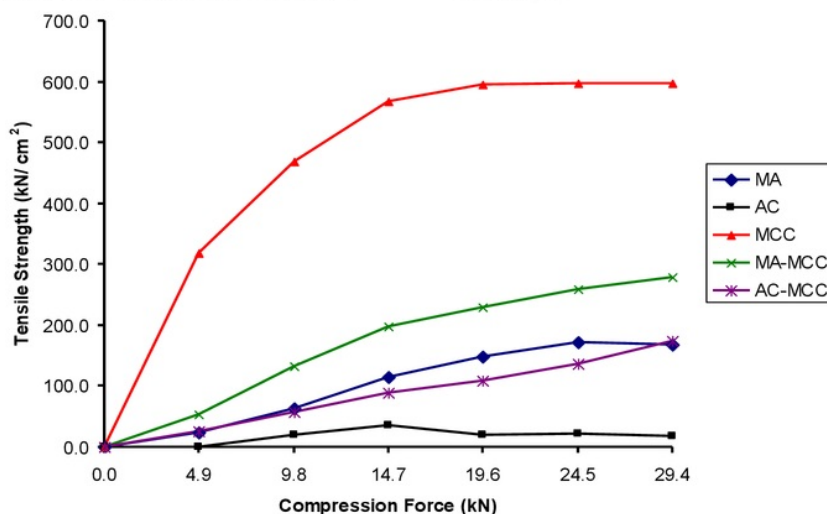


Fig. 7: Elastic modulus MA, AC, MCC, MA-MCC and AC-MCC.

From the elastic modulus curve, it was recognized that the tensile strength of MA is greater than AC, it indicates that the MA is more plastic than AC (Figure 7). Since MA is hydrophobic, AC is more elastic because the monoclinic crystals form. Enhancement of MA-MCC and

AC-MCC tensile strength compared with pure ingredients indicating that MCC can improve compactibility of MA and AC. Since MCC is a mixture of crystalline cellulose and porous agglomerate of microfibers, it could inhibit recrystallization of MA and AC [12,13,14].

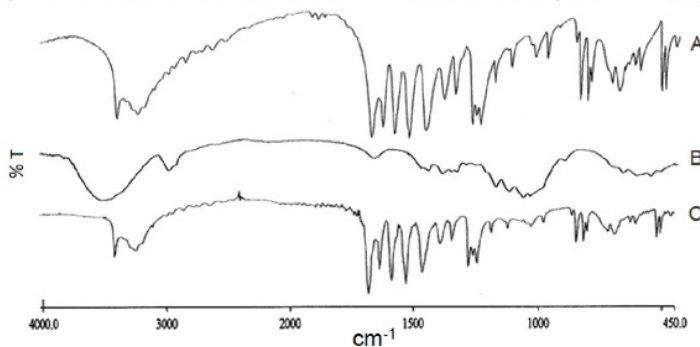


Fig. 8: Infra Red Spectra A.MA, B. MCC and C. MA-MCC (50:50) % w/w.

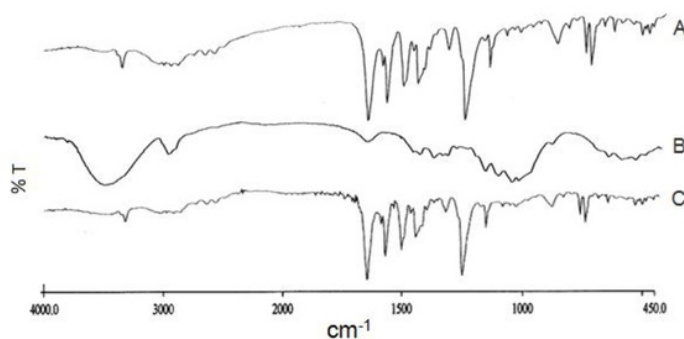


Fig. 9: Infra Red Spectra A.AC, B. MCC and C. AC-MCC (50:50) %w/w.



Figure 8 showed the FTIR spectrum of MA-MCC binary mixture along with the spectra of drug and MCC. MA spectrum presents peak at  $1503.41\text{ cm}^{-1}$  indicate its functional group, and a shift in the peak at  $1576.13$  and  $1651.33\text{ cm}^{-1}$  to  $1578.98$  and  $1610.25\text{ cm}^{-1}$  [15]. IR

spectra of MA-MCC depicted weakening and superposition between MA and MCC due to no interaction between MA with MCC. Fig. 9 demonstrated the FTIR spectrum of AC-MCC binary mixture, which gave similar result with MA-MCC.

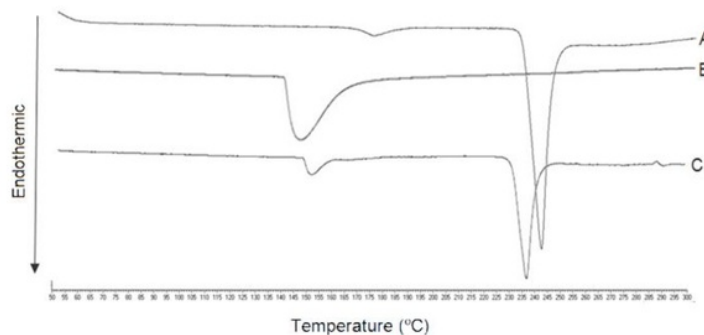


Fig. 10: Thermograms DTA A. MA, B. MCC and C. MA-MCC (50:50) % w/w.

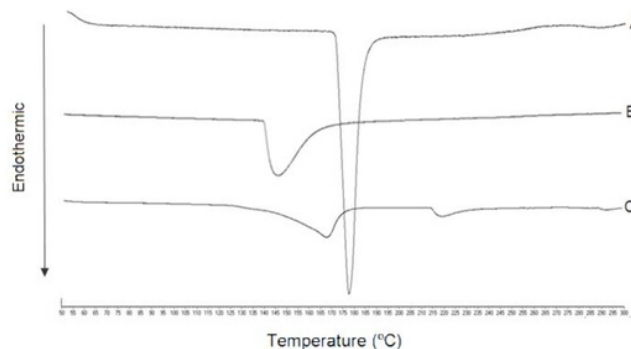


Fig. 11: Thermograms DTA A. AC, B. MCC and C. AC-MCC(50:50) % w/w.

DTA thermograms analysis results of MA-MCC showed that melting temperature and enthalpy of MA is  $172.2^{\circ}\text{C}$ ,  $171\text{ J/g}$  and  $232.7^{\circ}\text{C}$ ,  $9.27\text{ J/g}$  (Fig. 10). These two melting temperatures indicate the presence of two polymorphs MA. Polymorph form I at  $172.2^{\circ}\text{C}$  and form II at  $232.7^{\circ}\text{C}$  looked at the temperature of which is in line with the research that has been done [10]. Temperature and enthalpy MA-MCC mixture is  $169.8^{\circ}\text{C}$  and  $203.8^{\circ}\text{C}$ . In the MA-MCC mixture, melting temperature observed of each material with a slight shift of the melting temperature due to the influence of a mixture of one

another, there appeared to be no reaction between the two materials [16].

In Fig. 11 it was shown that melting temperature of AC is  $171.8^{\circ}\text{C}$  with enthalpy of  $219\text{ J/g}$ . In AC-MCC, it was detected two melting temperature at  $169.3^{\circ}\text{C}$  and  $198.4^{\circ}\text{C}$  conforming there was no reaction in AC-MCC mixture. Melting temperature at  $182.7^{\circ}\text{C}$  and  $198.4^{\circ}\text{C}$  on DTA thermograms of AC-MCC indicating transformation of polymorph form I to form II [2,17].

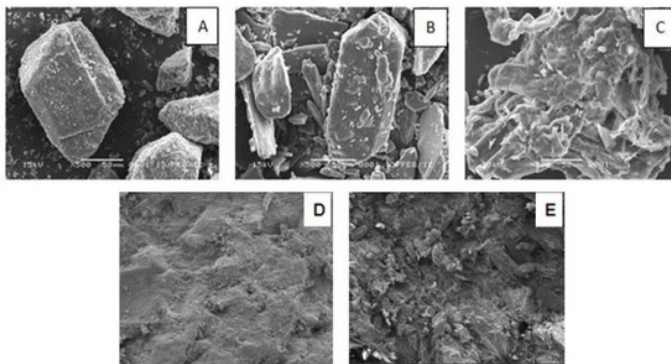


Fig. 12: Scanning electron micrographs of A. MA, B. AC, C. MCC, D. MA:MCC (50:50 %b/b) and E. AC: MCC (50:50 %b/b).

---- Bar =  $50\text{ }\mu\text{m}$ .

SEM was used to evaluate the surface of each substance and binary mixture [18]. From Fig. 12 it was observed MA has cube shape crystal, AC has monoclinic form and MCC forms of cellulose fibers. Upon compressed, binary mixture of MA-MCC has more compact form than AC-MCC that still reveal original crystalline form of AC.

# CONCLUSIONS

From this study, it was known that the intensity of X-ray powder diffraction AC and MA decreased as MCC amount increase. After compression mean crystallite size of the MA was 15-19 Å and AC is 21-30 Å respectively. MA has a better compactibility compared to the AC. It also known that there was no physical interaction between each drug substance with excipient after being compressed.

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